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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	
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12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,826	CASTERMAN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,22-36,51-56,59 and 64-69* is/are pending in the application.

4a) Of the above claim(s) *23,24,29 and 64-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,22,25-28,30-36,51-56 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/14/08 has been entered.

Applicant's amendment and response filed 10/14/08 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I and species of fragment of an immunoglobulin which is the variable region of a heavy chain, said variable region devoid of normal light chain interaction sites, and Applicant's election with traverse of the species of "labeled with a detectable label" that is "a radioactive label" in Applicant's response filed 1/23/06.

Claims 18, 19, 22, 25-27, 31-33, 35 and 51-54 read upon the elected species.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include the species recited in instant claim 22, *i.e.,* "immunoglobulin or a fragment thereof according to claim 19, which has a constant region which is devoid of a CH1 domain."

Upon consideration of prior art document EP 0584421 A1, examination has been extended to include the species of VHH recited in instant claims 28, 30, 34, 36, 55, 56 and 59.

Claims 18, 19, 22, 25-28, 30-36, 51-56 and 59 are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 18, 19, 22, 25-28, 30-36, 51-56 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. <u>This is a new matter rejection.</u>

The amendatory material not supported by the disclosure as originally filed is as follows: a variable region of a heavy polypeptide chain and a fragment of a variable region of a heavy polypeptide chain. Applicant has deleted the limitation "of an immunoglobulin" from the instant claims, creating more than one new genus.

5. For the purpose of prior art rejections, the filing date of the instant claims deemed to be the filing date of the instant application, *i.e.,* 1/5/04, as the parent applications do not support the claimed limitation of the instant claims as enunciated at item #4 supra of this Office Action. In addition, with regard to the instant claims that recite "a fragment of a variable region", the foreign priority documents do not support the limitation "a fragment [of] a variable region" of a heavy polypeptide chain that specifically binds an antigen of interest, said variable region being devoid of normal light chain interaction sites. EP 0584421 A1 which is the publication of EP application 92402326.0, one of Applicant's foreign priority documents, discloses fragments of variable region of heavy chain antibodies that are specific lengths only. In addition, the said EP document discloses only that the VHHs are devoid of light polypeptide chains, not devoid of normal light chain interaction sites (although some of those sites are disclosed in the EP document). Applicant does not point to support for the claim amendments as is required by MPEP 2163.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 22 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Ungar-Waron *et al* (Isr. J. Vet. Med. 1987, Vol. 43(3), pages 198-203, IDS reference) as evidenced by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference), Roux *et al* (PNAS USA 1998, Vol. 95, pages 11804-11809, IDS reference), WO 94/25591 (Applicant's IDS reference in the Form-1449 filed 7/24/06), and van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record).

Ungar-Waron *et al* teach a 40 Kd IgG from Camelid serum and composition thereof. Ungar-Waron *et al* teach that when camel serum was precipitated using ammonium sulfate, separated by DEAE-Sephacel, subjected to ultrafiltration, and analyzed by IEP and by SDS-PAGE two bands of 155 Kd and 100 Kd were visualized under non-reducing conditions, the 100Kd band dissociating into the 40 Kd band under reducing conditions upon SDS-PAGE analysis (especially Results and Discussion sections).

Evidentiary reference Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1

domain that binds to the light chain. Hamers-Casterman *et al* teach that the two 100 Kd immunoglobulin fractions yield only heavy chains of 46 Kd and 43 Kd upon reduction (see entire article, and especially second paragraph of article).

Evidentiary reference Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers (especially page 11804, column 2, paragraph before Materials and Methods section).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1 domain, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4). *WO 94/25591 teaches that this 100 Kd IgG like material is the same as taught by Ungar-Waron et al (the art reference cited in this rejection, see page 1 at lines 18-19 and page 4 at lines 31-32).*

Although the art reference Ungar-Waron *et al* does not teach that the 40 Kd IgG band from *Camelid* serum contains VHH lacking CH1 and devoid of light chains or binds antigens such as those recited in instant claim 53:

- evidentiary reference Hamers-Casterman *et al* teach the approximately 40 Kd size of the VHH lacking CH1 and devoid of light chains in *Camelid* serum upon reduction of the 100 Kd IgG that bind antigens in a lysate containing proteins, carbohydrates and nucleic acids from an infectious agent and that some *Camelids* have high anti-trypanosome titers,
- Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers, and
- WO 94/25591 teaches that the 100 Kd fraction of the art reference Ungar-Waron *et al* contains *Camelid* IgG heavy chains that lack light chains, lack the CH1 domain, and that these heavy chains bind antigens.

Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains (page 38 at the first full paragraph at column 1). van der Linden *et al* teach that unique features of VHH include the absence of both immunoglobulin light chains and the CH1 constant domain, and that *Camelid* VHH have been shown to retain immunoglobulin functions such as specific antigen binding (paragraph spanning pages 43-44).

With regard to the recitation of the variable region being devoid of normal light chain interaction sites, although the art reference Ungar-Waron *et al* does not teach that the *Camelid* IgG comprises a variable region devoid of normal light chain interaction sites, the evidentiary reference van der Linden *et al* teach that the *Camelid* variable fragments of the heavy chain antibodies do not have the hydrophobic interface which is important in the formation of a functional classical antibody molecule that is composed of heavy and light chains. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference EP 0739981 A1 teaches that the superior solubility of Camelid VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.,* that it is "suitable for use in *in vivo* diagnosis" recited in instant claim 32.

Claim 27 is included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 10/14/08 on pages 8-10.

Applicant argues that Ungar-Waron *et al* do not teach the variable region of a camel heavy chain.

However, instant claim 22 recites "A polypeptide comprising a variable region of a heavy polypeptide chain", and thus "comprising" encompasses a full heavy chain.

Applicant further argues that none of the proteins in Ungar-Waron are identified as IgG, and that WO 94/25591 does not teach anything about the properties of the 100 kD band of Ungar-Waron such as recited supra at bullet point #3, and thus does not teach that the isolated 100 kD proteins are the same as taught by Ungar-Waron.

The teaching of Ungar-Waron *et al* is of a 100 kD band that dissociates into a 40 Kd band under reducing conditions under SDS-PAGE analysis. The evidentiary references teach that the 100 Kd immunoglobulin fractions yield only heavy chains of the same size upon reduction, that the 100 Kd IgG in camel serum is composed of heavy chain dimers that are devoid of light chains that lack the CH1 domain, that the approximately 40 Kd molecules are IgG2 and IgG3 classes that lack the light chain. Evidentiary reference WO 94/25591 teaches that the 100 Kd IgG material is the same as taught by Ungar-Waron *et al*, thus establishing that the 40 Kd material taught by Ungar-Waron *et al* is a *Camelid* heavy chain devoid of light chains. WO 94/25591 teaches "The presence of considerable of amounts of IgG like material of 100 Kd in the serum of the camel (*camelus dromedarius*)(6) was confirmed. These molecules are composed of heavy chain dimers and are devoid of light chains. Nevertheless they bear an extensive antigen binding repertoire…Camel heavy chain IgGs lack the CH1...". Thus, the 40 Kd protein is a fragment of the 100 Kd protein that is a *Camelid* antibody comprised of two heavy chains devoid of light chains.

The art meets the claim limitations.

8. Claims 22 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Grover *et al* (Ind. J. Biochem. Biophys. 1983, 20(4): 238-240, IDS reference filed 7/24/06, of record) as evidenced by WO 94/25591 (IDS reference filed 7/24/06) and van der Linden *et al* (Biochimica *et* Biophysica Acta 1999, 1431: 37-46, of record).

Grover *et al* teach camel IgG2 isotype polyclonal antibodies, including in reduced form. Grover *et al* teach that polyacrylamide gel electrophoresis of ammonium sulfate precipitated camel serum immunoglobulins was done as described by Satija *et al* (Inf. Immun. 1979, 24(2): 567-570) (especially pages 238-239 of Grover *et al*).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that

camel heavy chain IgGs lack the CH1, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4).

Evidentiary reference Satija *et al* teach that polyacrylamide electrophoresis involved staining the gel with a solution of amido black in HAc (*i.e.,* labeled with a detectable label that is a chemical marker as recited in instant claims 33 and 35, respectively, materials and methods section).

Although the art reference Grover *et al* does not teach that the IgG2 istoype antibody from *Camelid* serum contains VHH lacking CH1 and devoid of light chains, or binds antigens such as those recited in instant claim 53, evidentiary reference WO 94/25591 teaches that the *Camelid* IgG2 heavy chains lack light chains and that these heavy chains bind antigens. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).
Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains (page 38 at the first full paragraph at column 1). van der Linden *et al* teach that unique features of VHH include the absence of both immunoglobulin light chains and the CH1 constant domain, and that *Camelid* VHH have been shown to retain immunoglobulin functions such as specific antigen binding (paragraph spanning pages 43-44).

With regard to the recitation of "variable region being devoid of normal light chain interaction sites", although the art reference Grover *et al* does not teach that the IgG2 istoype antibody from *Camelid* serum comprises a variable region that is devoid of normal light chain interaction sites, the evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain and that the variable fragments of these heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a

showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 27 is included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 10/14/08 on pages 8-10.

Applicant argues that Grover *et al* do not teach the variable region of a camel heavy chain.

However, instant claim 22 recites "A polypeptide comprising a variable region of a heavy polypeptide chain", and thus "comprising" encompasses a full heavy chain.

9. Claims 18, 19, 22, 25-27, 31-33, 35, 51-53, 55 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21, of record).

Frenken *et al* teach VHH fragments of *Camelid* antibodies specific for a hapten, and that these fragments may be produced in a eukaryotic host cell such as the yeast *S. cerevisiae*. Frenken *et al* teach these fragments labeled with an enzymatic marker or with a chemical marker or with a c-myc tag (see entire reference, especially abstract, introduction, sections 2.2 and 3.3 and discussion).

Claims 31 and 32 are included in this rejection because the intended uses of the product "suitable for use in "*in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis," respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference teaches samples of culture media containing secreted VHH fragments, *i.e.,* a "composition".

Claims 26 and 52 are included in this rejection because Frenken *et al* teach a fragment of one of the VHHs that binds antigen (Section 3.3).

Claim 59 is included in this rejection because it is an inherent property of the VHH that it is capable of targeting drugs, hormones or cytokines to cells.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 10/14/08 on page 11.

Applicant argues that Frenken *et al* was published after the priority date of the instant application.

However, the instant claims have the priority date of the instant application as enunciated supra, and hence Frenken *et al* is available as prior art.

10. Claims 18, 19, 22, 25, 27, 31-34, 35, 51, 53, 55 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520, of record).

Lauwereys *et al* teach single chain *Camelid* antibodies, devoid of normal light chain interaction sites, as well as variable domain fragments of said antibodies, including wherein the fragments are labeled with a chemical marker (on SDS-PAGE) or with an enzymatic marker (in ELISA), or monomeric heavy chains of the Camelid IgG2 and IgG3 antibodies that are devoid of light chains, including labeled with a chemical marker (on SDS-PAGE) (see entire reference).

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference teaches phage display and also liquid compositions comprising a *Camelid* VHH single domain fragment *i.e.,* a "composition comprising a variable region of a heavy polypeptide chain…"

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Claim 59 is included in this rejection because it is an inherent property of the VHH that it is capable of targeting drugs, hormones or cytokines to cells.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 10/14/08 on page 11.

Applicant argues that Lauwereys *et al* was published after the priority date of the instant application.

However, the instant claims have the priority date of the instant application as enunciated supra, and hence Lauwereys *et al* is available as prior art.

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

11. Claims 18, 19, 22, 25-28, 30-36, 51-56 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0584421 A1.

EP 0584421 A1 teaches VHH fragments of heavy chain antibodies from *Camelids* as well as fragments of the variable region of the *Camelid* antibodies that are at least 10 or at least 20 amino acids in length. EP 0584421 A1 also teaches the entire heavy chain antibody that comprises a constant region devoid of the CH1 domain (especially claim 16). EP 0584421 A1 teaches the antibodies or fragments thereof against proteins, haptens, carbohydrates or nucleic acids , or labeled with a detectable label such as an enzymatic marker, a radioactive marker, technetium (an imaging agent), a chemiluminescent marker, a drug, a hormone, a cytokine, or a toxin such as mistletoe lectin toxin, the constructs being capable of targeting the added toxin, drug, hormone or cytokine. EP 0584421 A1 teaches a modified four-chain immunoglobulin or fragment thereof in which the VH regions have been partially replaced by specific sequences or amino acid residues of VHH (especially page 10, page 11 at the first thirty lines). EP 0584421 A1 teaches a fragment of a variable region which comprises at least 10 amino acid residues of the VHH and comprises a charged amino acid residue or cysteine at position 45 (especially page 5 at lines 24-37, claim 16). EP 0584421 A1 teaches that the specificity of the VHH can be anti-idiotypic (especially page 6).

With regard to the claims that recite “recombinantly fused to a constant region”, the method by which the polypeptide is made carries no patentable weight per se in the absence of a structural difference.

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin “suitable for use in *in vitro* diagnosis” or “suitable for use in *in vivo* diagnosis”, respectively, do not carry patentable weight per se.

12. Claims 18, 22, 25, 27, 28, 30-35, 51, 53, 54 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Cortex-Retamozo *et al* (Int. J. Cancer, 2002, 98: 456-462).

Cortex-Retamozo *et al* teach a VHH antibody fragment or a bivalent construct thereof, and including labeled with a radioactive label, and the specificity of the VHH antibody fragment is directed against a transfected protein present on the surface of a tumor cell (see entire reference).

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 18, 19, 33-35, 51- 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21, of record) or EP 0584421 A1 in view of Power and Hudson (Expert Opin. Biol. Ther. 2003, 3(2): 385-389).

The primary references Frenken *et al* or EP 0584421 A1 have both been discussed supra.

These primary references do not teach wherein the variable region or the fragment thereof specifically binds a protein present on tumor cells.

Power and Hudson teach proteins on the surface of tumor cells that are targets for antibody therapy (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art to generate a VHH antibody or fragment thereof such as taught by Frenken *et al* or by EP 0584421 A1 having specificity for a tumor target protein such as taught by Power and Hudson, and to have included them in a composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for tumor therapy.

Furthermore, Power and Hudson teach designing these antibodies with radionuclides, toxins, enzymes, and drugs for clinical diagnosis and therapy (especially abstract and conclusion).

It would have been prima facie obvious to one of ordinary skill in the art to make an immunoconjugate such as taught by Power and Hudson using the antibody composition of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for diagnosis and therapy.

15. Claims 18, 33-35, 51, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520, of record) in view of Power and Hudson (Expert Opin. Biol. Ther. 2003, 3(2): 385-389).

The primary reference Lauwereys *et al* has been discussed supra.

The primary reference does not teach wherein the variable region specifically binds a protein present on tumor cells.

Power and Hudson teach proteins on the surface of tumor cells that are targets for antibody therapy (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art to generate a VHH antibody fragment such as taught by Lauwereys *et al* having specificity for a tumor target protein such as taught by Power and Hudson, and to have included it in a composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for tumor therapy.

Furthermore, Power and Hudson teach designing these antibodies with radionuclides, toxins, enzymes, and drugs for clinical diagnosis and therapy (especially abstract and conclusion).

It would have been prima facie obvious to one of ordinary skill in the art to make an immunoconjugate such as taught by Power and Hudson using the antibody composition of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition for diagnosis and therapy.

16. The terminal disclaimer filed on 10/14/08 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on U.S. Application Serial No. 11/350,900 has been reviewed and is accepted. The terminal disclaimer has been recorded.

17. Applicant's terminal disclaimer filed 10/14/08 has over come the rejection of claims 18, 19, 22, 25-27, 31, 32 and 51-54 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-27 and 33 of copending Application No. 11/350,900 in view of van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record).

18. Applicant's terminal disclaimer filed 10/14/08 has over come the rejection of claims 33 and 35 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-27 and 33 of copending Application No. 11/350,900 in view of van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record) as applied to claims 18, 19, 22, 25-27, 31, 32 and 51-54, and further in view of Harlow and Lane (of record).

19. Claims 18, 19, 22, 25-28, 31-36, 51-56 and 59 are objected to because of the following informality: the limitation "of an immunoglobulin" has been deleted from base claims 18, 19, 22, 51 and 52, following "a variable region of a heavy polypeptide chain" or following "a fragment of a variable region." Appropriate correction is required.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Group 1640
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December 12, 2008

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644